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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/316,199	05/21/99	MCCLUSKIE M	C1040/7006HC

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/316,199	Applicant(s) MCCLUSKIE ET AL.	
	Examiner Dave Nguyen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28,66,73,77,81,85,89 and 93* is/are pending in the application.

4a) Of the above claim(s) *29,47,66,73,77,81,85,89 and 93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,7,12* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Claim 1 has been amended by the response filed March 29, 2001.

Applicants in the Response filed March 29, 2001 elected Invention of Group 1, claims 1-28 with traverse. The traversal (page 2) is that there is no undue burden to search all of the inventions as restricted in the Group inventions. The traversal is not found persuasive because of the reasons set forth in the previous restriction letter. The restriction therefore is proper and final. Claims 29, 47, 66, 73, 77, 81, 85, 89, 93, 109, and non-elected species (species of claims 9, 11, 13 and 23) remain withdrawn from consideration, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

After a search of prior art and further consideration, the species restriction with respect to cytokine and alum, and the species restriction requirement between intranasal and oral administration have been withdrawn by the examiner because the below stated rejections are applicable to claim limitations of cytokine and/or alum and of nasal and oral administrations.

Citation of Reference C14 in the IDS filed Feb. 17, 2000 is objected because the citation lacks the publication dated. Citation of Reference C4 in the IDS filed March 20, 2000 is objected because the citation lacks the publication dated. Note that all filed IDS should be check or completeness should the application be issued as a patent so as to devoid delay in printing.

The contents of the PCT search report has been considered but its citation in the IDS has not been initiated by the examiner because the report is not a prior art publication.

Elected claims 1-10, 12, 14-22 and 24-28 readable on species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T as a species of CpG motif, the species of colloidal dispersion system, the species of alum as non-oligo mucosal adjuvant, the species of subject at risk of developing an infectious disease, the species of infectious virus as a species of antigen, the species of intranasal route, to which the following grounds of rejection are applicable, are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12 and 14-22 and 24-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing a mucosal immune response, comprising:

Administering to a mucosal surface of a subject an effective amount for inducing a mucosal immune response of an oligonucleotide having a length of least 8 nucleotide residues and comprising CpG motif containing oligonucleotide including the elected species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T; and administering to the subject an antigen not encoded in a nucleic acid vector to the subject to induce the mucosal immune response, does not reasonably provide enablement for methods of administering any CpT motif containing oligonucleotide of less than 8 nucleotide residues including the elected species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T for inducing a mucosal immunity to a recombinant peptide/polypeptide antigen within the context of therapeutic applications.

With respect to the preamble of claim 1 and claims dependent therefrom, the presently pending claims encompass a method of "exposing" any subject including mammals, insects, reptiles, birds that is at risk of developing an infectious disease, *e.g.,* viral infection, it is apparent to a skilled artisan on the basis of applicant's disclosure that in order to carry out the step of "exposing", the essential feature or step of administering an antigen to the claimed subject must be carried. Without the essential step of the "administering by inhalation", for example, it is not apparent as to how a skilled artisan to carry out the "exposing" as intended by applicant in the claims particularly on the basis of applicant's disclosure.

With respect to claimed invention directed to inhalation of any CpT motif containing oligonucleotide of less than 8 nucleotide residues including the elected species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T for inducing a mucosal immunity to a recombinant peptide/polypeptide antigen within the context of therapeutic applications, the

specification only provides sufficient guidance and/or factual evidence demonstrating an increase of an mucosal immunity in mice wherein a CpG containing oligo of 20 nucleotide residues is employed. However, given that any inhalation of any naked DNA including CpG containing oligo has to overcome immune barriers including the presence of nucleases, it is not apparent as to how a skilled artisan would reasonably conclude on the basis of applicant's disclosure that any CpG containing oligo regardless of the length would operate as intended by the as-filed specification, nor is it apparent as to how a skilled artisan would reasonably extrapolate, without any undue experimentation, from applicant's disclosure to the full breadth of the claims.

Thus, it is not apparent how one skilled in the art, without undue experimentation, practices the elected claimed invention on its full breadth, and/or uses the methods as claimed to provide an active mucosal immunity for future protection and/or therapeutic efficacy against an infection by a virus, particularly on the basis of applicant's disclosure and the breadth of the claims, and in view of the doubts expressed in the art of record at the time the invention was made.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 10, 4, 8, 20, 26, 27 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and 10 are indefinite in the recitation of "exposing", "exposing passively" and "exposing passively", respectively, because it is not apparent as to the what are exactly the material(s) or step(s) are carried out achieve the "exposing".

Claims 2, 8 and 26-28 are indefinite because it is not apparent as to where the "administering" occurs.

Claim 20 is indefinite in the recitation of "such as" because the "such as" does not indicate *per se* as to what is exactly the intended scope of the claim, particularly since "multicellular organisms" include mammals, insects, reptiles.

Claim 26 is indefinite because it is not apparent as to what exactly the intended meaning of "remote". The claim does not contain any recitation of a standard to describe the relative meaning of "remote site".

Claim 27 is indefinite because it is not apparent whether or not "a boost oligonucleotide" refers to the previously administered oligo or other oligonucleotides. The lack of the article "a" or "the" renders the claim vague and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-7, 10, 12, and 14-22 and 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Krieg (WO 96/02555), as evidenced by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998 (cited in PCT search Report as indicated in the IDS), Sato *et al.* (US Pat No. 6,090,791), McCluskie *et al.* (IDS, C2), and Mestecky *et al.* (Genetically Engineered Vaccines, 1992, IDS, C33).

The essential feature of the presently pending claims is that a mucosal immunity would be elicited by a combination administration to the mucosal surface of any subject, *e.g.,* oral administration, of any known antigen (not in the form of a nucleic acid sequence) and an oligonucleotide (which can be complexed with any known colloidal dispersion system including lipid based system) having a length of

least 8 nucleotide residues and comprising CpT motif containing oligonucleotide including the elected species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T. Krieg teaches identical concept throughout the disclosure (pages 7, 10, 11, 13 and 14,for example). More specifically, on pages 21 and 22, oral administration of the oligo and/or antigen is disclosed. CpG motifs including 5' GTCpGTT is also encompassed by the disclosure of Krieg. Example 8 of Krieg also indicates that IL-6 production is elicited by an injection of a CpG motif containing oligo to mice. In view of the factual evidence established by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791) McCluskie *et al.* (IDS, C2) which shows that CpG motifs when administered to the mucosal surface of a subject does generate an mucosal immunity, and by Mestecky *et al.* which demonstrate local production of IL-6 at the mucosal surface does stimulate production of IgA antibodies, the method of Krieg would inherently generate production of mucosal immunity, particularly in view of the absence of evidence to the contrary.

Claims 1-10, 12, 14-22, and 24-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieg *et al.* (US Pat No. 6,218,371), as evidenced by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791), McCluskie *et al.* (IDS, C2), and Mestecky *et al.* (Genetically Engineered Vaccines, 1992, IDS, C33).

The essential feature of the presently pending claims is that a mucosal immunity would be elicited by a combination administration to the mucosal surface of any subject, *e.g.,* oral administration or intranasal administration, of any known antigen (not in the form of a nucleic acid sequence) and an oligonucleotide (which can be complexed with any known colloidal dispersion system including lipid based system) having a length of least 8 nucleotide residues and comprising CpT motif containing oligonucleotide including the elected species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T. Krieg *et al.* teach the same throughout the disclosure (columns 15, 18-20, 23-28, 31 and 32). More specifically, on column 31, oral administration and nasal administration of the oligo and/or antigen is disclosed. CpG motifs including 5' GTCpGTT is also disclosed on columns 3, 4 and 23. The use of a colloidal dispersion system is disclosed on column 19. The use of a cytokine including B-7 as an adjuvant in combination with the CpG containing oligo of at least 8 nucleotides is disclosed on

column 25, 26 and 29, for example. IL-6 production is also disclosed on Example 7. In view of the factual evidence established by Moldoveanu *et al.*, Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791) McCluskie *et al.* (IDS, C2) which shows that CpG motifs when administered to the mucosal surface of a subject does generate an mucosal immunity, and by Mestecky *et al.* which demonstrate local production of IL-6 at the mucosal surface does stimulate production of IgA antibodies, the method of Krieg *et al.* would inherently generate production of mucosal immunity, particularly in view of the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 12, 14-22 and 24-28 are rejected under 35 U.S.C. 103 as being unpatentable over either Krieg (WO 96/02555) or Krieg *et al.* (US Pat No. 6,218,371), taken with Krieg *et al.* (Trends In Mircobiology, Vol. 6, No. 1, pp. 23-27, 1998), as evidenced by Moldoveanu *et al.*, Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791), McCluskie *et al.* (IDS, C2), and Mestecky *et al.* (Genetically Engineered Vaccines, 1992, IDS, C33).

The rejection of claims 1-7, 10, 12, and 14-22 and 26-27, as being anticipated by either Krieg or Krieg *et al.*, as evidenced by Moldoveanu *et al.*, Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791), McCluskie *et al.* (IDS, C2), and Mestecky *et al.* (Genetically Engineered Vaccines, 1992,

IDS, C33), is applied here as indicated above. To the extent that the references do not teach the use of Th2 response induced-adjuvant including alum in the methods, Krieg (Trends In Mircobiology) is one of many references which teach that alum is effective as an Th2 response induced adjuvant which is the only one approved for human use in combination with antigen vaccines.

Thus, it would have been obvious for one of ordinary skill in the art to have employed alum in the immunization methods of either Krieg or Krieg *et al.* One of ordinary skill in the art would have been motivated to have employed alum as an adjuvant in the methods of Krieg or Krieg *et al.* because Krieg (Trends In Mircobiology) is one of many references which teach that alum is effective as an Th2 response induced adjuvant which is the only one approved for human use in combination with antigen vaccines. Note that it is well established that an mucosal immunity the same as Th2 response.

Thus, the claimed invention as a whole was *prima facie* obvious.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Kimberly Davis, whose telephone number is **(703) 305-3015**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Clark*, may be reached at **(703) 305-4051.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Patent Examiner
Art Unit: 1633

DAVE T. NGUYEN
PRIMARY EXAMINER